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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/526,851	05/19/2005	Alan P. Kozikowski	234590	5465

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EXAMINER	
NOLAN, JASON MICHAEL	
ART UNIT	**PAPER NUMBER**
1626	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/526,851	KOZIKOWSKI ET AL.	
	Examiner	Art Unit	
	Jason M. Nolan, Ph.D.	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05/15/2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-38 and 53-69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-17,28,37,38,53-59 and 64-69* is/are rejected.

7)☒ Claim(s) *18-27 and 29-36* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 3-38 & 53-69 are pending in the instant application; of which, **Claims 1 & 38** are currently amended, and **Claims 56-69** are new.

Response to Amendment

Applicant's amendments, see Amendment – After Non-Final Rejection, filed 05/15/2007, with respect to **Claims 1 & 38** have been fully considered and are entered. The 102-prior art rejections of Teraji *et al.*; Kokusho *et al.*; Vizitiu *et al.*; and Ryan *et al.* have been withdrawn per provisos in the claim language.

The rejections of Qiao *et al.* and Hu *et al.* are withdrawn per proviso; however, not the proviso stated in Applicants reply, (*see* page 10), wherein Applicant states the compounds of Qiao *et al.* and Hu *et al.* are avoided because $\mathbf{R_2}$, $\mathbf{R_3}$, $\mathbf{R_5}$ & $\mathbf{R_6}$ are not simultaneously OH. That proviso does not apply to compounds RN 213388-41-1, RN 213388-42-2, and RN 253440-95-8 because in each of the three compounds there is a CH_2 in the ring that can be defined as either $\mathbf{R_3}$ or $\mathbf{R_5}$. Depending on which way you look at the prior art structures: if the CH_2 ring variable is at position **5**, then the proviso does not apply; but if the CH_2 ring variable is at position **3**, then the proviso wherein if **X** = O, **Y** = O or CH_2 and $\mathbf{R_3}$ is H, then one of $\mathbf{R_2}$ and $\mathbf{R_4}$-$\mathbf{R_6}$ is not OH would apply; therefore, excluding said compounds.

Inasmuch, in order to exclude compounds of the prior art from the instant application via one of the provisos in formula I, then any and/or all of the provisos would have to be applied to the structure of each prior art compounds by assigning the ring

positions both clockwise and counterclockwise. Likewise, the potential patent protection for the instant application would have to be applied in the same manner to the compounds of the instant disclosure.

Claim Rejections - 35 USC § 102

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 3-17, 28, 37, 38, 53-59 & 64-69 are rejected under 35 U.S.C. 102(b) as being anticipated by Teraji *et al.* (*see* US Patent 4,585,762, 04/29/**1986**). Specifically, shown in column 6 is compound D, wherein **X** = O; **Y**= O; **A** = P(O)OH; $\mathbf{R_7}$ = C_1 alkyl; $\mathbf{R_1}$ = C_{18} alkyl; $\mathbf{R_2}$ = C_1 alkyloxy; and $\mathbf{R_3}$-$\mathbf{R_6}$ = OH. Said compound directly anticipates formula I and avoids the provisos therein. Furthermore, as pointed out in the abstract, the compounds in the **'762** Patent are useful in exhibiting antitumor activity, (**Claims 37, 56, 57, 66 & 69**). Although the patent is silent with respect to: 1) inhibiting activation of the serine/threonine kinase Akt or decreasing phosphorylation in a tumor cell, (**Claims 38 & 68**); 2) increasing apoptosis of a cell, (**Claims 53 & 64**); and 3) a method for inhibiting PH domain, (**Claims 55 & 65**); all of these properties would be expected and/or inherent in a compound that directly anticipates formula I and, further, has been tested for antitumor activity (*see* the results in column 7 of the **'762** patent.

Claim Rejections - 35 USC § 112, 1st

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 58 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound according to formula (I) in **Claim 58** wherein: **A** = P(O)OH, it does not reasonably provide enablement for a compound having the structure in **Claim 58** wherein **A** = CHCOOH or $C(COOH)_2$. Further, while being enabling for a compound according to the formula (I) wherein: $\mathbf{R_2}$-$\mathbf{R_6}$ = H, OH, etc. it does not reasonably provide enablement for a compound having the structure in **Claim 58** wherein $\mathbf{R_2}$-$\mathbf{R_6}$ = isosteres of OH. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in *In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)*. A conclusion of lack of enablement means that, based on the evidence regarding a fair evaluation of an appropriate combination of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

These factors include:

(A) *The breadth of the claims;*
(B) *The nature of the invention;*
(C) *The state of the prior art;*
(D) *The level of one of ordinary skill;*
(E) *The level of predictability in the art;*
(F) *The amount of direction provided by the inventor;*
(G) *The existence of working examples; and*
(H) *The quantity of experimentation needed to make or use the invention based on the content of the disclosure.*

The breadth of the claims - The nature of the invention

The currently pending invention is drawn to compounds and compositions according to the formula (I), wherein the definitions of **X, A, Y & R_1-R_7** are defined therein. Compounds according to this formula are useful for blocking activation of the proto-oncogenic serine/threonine kinase Akt (also known as RAC-PK or protein kinase B (PKB)), and therefore potentially inducing cancer cell apoptosis.

In the case of isosteres in medicinal chemistry, the following is understood: (a) isosterism is defined as compounds or groups of atoms having the same number of atoms and electrons, and (b) the -OH functional group is commonly replaced by isosteres -NH_2 or -SH. (Note: no definition or examples of isosteres has been provided in the specification)

The state of the prior art

A review of the literature provided by Applicant in the Information Disclosure Statement (IDS) and the CAS structure search results suggests that the state of the prior art is more advanced for species in which **A** = P(O)OH or C=O, whereas no species have been described wherein **A** = CHCOOH or $C(COOH)_2$. Likewise, there are

numerous examples wherein $\mathbf{R_2}$-$\mathbf{R_6}$ = H, OH, OAc, OBn, and salts such as -NMe_3 or –OPO_3H_2. However, no examples exist wherein the -OH functional group is commonly replaced by the isosteres -NH_2 or -SH.

The level of predictability in the art

The synthesis of complex natural products is an integral part of modern organic chemistry, however, even the synthesis of molecules or molecular fragments containing ten carbons or less can also pose great challenges. Examination of many synthetic endeavors, large and small, reveals that formation of the carbon skeleton by carbon-carbon bond forming reactions requires the most strategic planning. The largest number of actual chemical reactions in a synthesis, however, usually involves manipulation of functional groups (Smith, M. B. Organic Synthesis, McGraw-Hill, Inc. **1994**, Chapter 1). The functional group substitution of **A** from P(O)OH or C=O to CHCOOH or $C(COOH)_2$, and of $\mathbf{R_2}$-$\mathbf{R_6}$ from OH to -NH_2 or -SH changes the necessary starting materials for making these compounds as well as the predictability of their chemical reactivity. The functional group difference influences the bond length, electronegativity, and therefore the localization of electrons with respect to the functionality, which results in a lack of said predictability in their preparation. The art is silent with regard to the predictability of *any* compound as set forth by the formula (I) in with respect to its preparation, isolation, and use for treatments, therefore a change in **A** or $\mathbf{R_2}$-$\mathbf{R_6}$ would not only effect the chemical properties of the reagents for producing the desired products, but inherently also effect the desired biological properties for this

class of compounds. Therefore, it is unpredictable to know, from the outlined methods in the instant specification, how to make and use *all* of the compounds instantly claimed in formula (I).

The amount of direction provided by the inventor

The instant specification is not seen to provide adequate guidance, which would allow the skilled artisan to extrapolate from the disclosure and examples provided, to make the claimed invention commensurate in the scope with the instant claims. There is a lack of information pertaining to the synthesis of all compounds according to formula (I) in which **A** = CHCOOH or $C(COOH)_2$ or for compounds in which $\mathbf{R_2}$-$\mathbf{R_6}$ = isosteres of -OH. The direction provided does not adequately represent the scope of **Claim 58** as written. The Examiner points out that all of the compounds in the schemes and as well as the synthetic procedures described in the specification provide guidance to the invention only when **A** = P(O)OH and $\mathbf{R_2}$-$\mathbf{R_6}$ = H, OH, OBn, etc.

The existence of working examples

The working examples set forth in the instant specification are directed to the compounds of the formula (I) for which **A** = P(O)OH and $\mathbf{R_2}$-$\mathbf{R_6}$ = H, OH, OBn, etc. There has not been provided sufficient evidence that would warrant the skilled artisan to accept the data and information provided in the working examples as correlative proof that any compound of formula (I) would indeed be able to be synthesized and used by means of the methods outlined in the specification.

The quantity of experimentation needed to make and use the invention based on the content of the disclosure

In view of the information set forth supra, the instant disclosure is not seen to be sufficient to enable the preparation of any compound of formula (I) as defined. One skilled in the art could not use the entire scope of the claimed invention without undue experimentation. Undue experimentation would include, for instance: the preparation of multiple synthetic outlines for each of the different definitions of **A** and $\mathbf{R_2}$-$\mathbf{R_6}$; the preparation of the necessary starting materials required for each of the compounds according to the formula (I) wherein **A** are CHCOOH or $C(COOH)_2$ and $\mathbf{R_2}$-$\mathbf{R_6}$ are isosteres of -OH, followed by attempts to prepare a desired product for each of the different functional groups, subsequently followed by isolation, characterization, and testing the various compounds to determine if indeed they had utility for the treatment of various diseases.

Claims 56 & 67 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while enabling for compounds and compositions that inhibit tumor growth in certain cancers, does not reasonably provide enablement for treating any and/or all types of cancer. For instance, the 1.132 affidavit submitted by Applicant, 05/15/2007, discloses a compound (SH-23) that inhibits growth of certain cancer cell lines but not others). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The nature of the invention

The currently pending invention is drawn to compounds and compositions according to the formula (I), which are useful for inhibiting growth of certain cancer cell lines.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art, namely pharmacological art, involves screening *in vitro* and *in vivo* to determine if the compounds exhibit desired pharmacological activities, which are then tested for their efficacy on human beings. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. The instant claimed invention is highly unpredictable as discussed below.

In the instant case, the claimed invention is highly unpredictable since one skilled in the art would recognize that a group of compounds and compositions may treat certain cancers, however, it does not mean that the same group of compounds and compositions may treat any and/or all types of cancer.

A recent review by Kumar *et al.* (*Oncogene* **2005**, *24*, 7493-7501) establishes the Akt crystal structure and a rationale for targeting Akt for new drug discovery. It is now well established that hyperactivation of Akt kinases is a common event in human cancers, and this activation results in tumor cell survival and enhanced resistance to apoptosis through multiple mechanisms (p. 7493). It is also established that small molecule inhibitors of Akt provide a platform for therapy, albeit via different biological mechanisms. For example, compounds can target the Atp binding pocket, the PH domain, LINK and the protein substrates (p. 7496). The compounds of the instant case target the PH domain are discussed on page 7499. These compounds inhibited Akt activation and phosphorylation of several downstream substrates of Akt in tumor cells without affecting the activities of upstream kinases. Kumar explains, "Significantly these analogs increased apoptosis 20- to 30-fold in tumor cell lines expressing high levels of endogenous activated Akt and were only modestly active in tumor cells expressing low levels of activated Akt. *Major issues* with this class of molecules are limited solubility, moderate potency against Akt kinases, aggregation and poor pharmacokinetics, *which limit their usefulness as small molecule drug leads*. Moreover, it is not clear how specific these compounds are towards blocking Akt translocation to the membrane, since PH domains are present in several proteins." The crystal structure has been solved for the complex of Akt1 PH domain with inositol tetraphosphate and this binding pocket is *not an ideal drug target* because it is shallow and highly charged.

The amount of direction or guidance present and the presence or absence of working examples

There is no direction or guidance provided which supports Applicant's claimed method for treating any and/or all types of cancer, as indicated. The direction or guidance present in Applicants' Specification details a method of inhibiting Akt activation and is found on pages 13-15. Furthermore, the 1.132 affidavit submitted by Applicant, 05/15/2007, discloses a compound (SH-23) that inhibits growth of certain cancer cell lines: (non small cell lung cancer (HF22, H23); CNS/brain (U251, SF-295); breast (MDA-MB-231, MDA-MB-435); ovarian (OVCAR-5); colon (SW 620); and pancreatic (LOX); but not others: melanoma (UACC-62), CNS/brain (U251); and colon (SW 620, COLO205).

This makes sense because according to this invention the compounds of the instant application target Akt, which is not present in all cancer types at the same concentration level. Stated by Kumar *et al.*: "Significantly these analogs increased apoptosis 20- to 30-fold in tumor cell lines expressing high levels of endogenous activated Akt and were only modestly active in tumor cells expressing low levels of activated Akt."

The breadth of the claims, quantity of experimentation, and level of skill in the art

Because of the major issues identified in the Kumar reference, a person of skill in the art could not practice the claimed invention herein, or a person of skill in the art

could practice the claimed invention herein only with undue experimentation and with no assurance of success.

The Examiner suggests incorporating the specific types of cancers listed in **Claim 57 & 69** into **Claims 56 & 67**, respectively.

Claim Objections

Claims 31 & 34 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Specifically, the compound of **Claim 31** wherein **R_2, R_3, R_5 & R_6** are OH is excluded from formula I in proviso (iv). Specifically, the compound of **Claim 34** wherein **R_4 & R_5** are simultaneously H is excluded from formula I in proviso (iii).

Claims 18-27, 29-36 & 60-63 are objected to as being dependent upon a rejected base, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jason M. Nolan, Ph.D.** whose telephone number is **(571) 272-4356** and electronic mail is **Jason.Nolan@uspto.gov**. The examiner can normally be reached on Mon - Fri (9:00 - 5:30PM). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph M^{c}Kane** can be reached on **(571) 272-0699**. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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